UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	December 16, 2008
LISZIEWICZ, et al.	:	Atty Docket No. RGT 9771
Serial No. 10/081,922	:	Group 1632
Filed: 15 September 1998	:	Examiner: Wilson

For: **Method of Delivering Genes into Antigen Presenting Cells of the Skin**

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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BRIEF ON APPEAL[1]

Following a Notice of Appeal filed October 16, 2008 together with a petition for a three-month extension of time, kindly enter the enclosed Brief of record. A credit card form for the fee set forth in § 41.20(b)2 is enclosed. The Commissioner is authorised to charge any additional fees due, or credit any overage, to Deposit Account No. 50-0855.

The applicant remains entitled to the previously-claimed small entity status.

Respectfully Submitted,

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[1] This paper is being forwarded by fax to the Commissioner of Patents, P.O. Box 1450 Alexandria, VA 22313-1450 on December 16, 2008. Signed Valerie E. Looper Valerie E. Looper

REAL PARTY IN INTEREST

The real party in interest in this case is Genetic Immunity, Inc., a Delaware corporation having an office at 8300 Greensboro Drive, McLean Virginia 22102.

RELATED CASES

As of December 16, 2008, there are no appeals and interferences related to this case. A Notice of Appeal was previously filed in this case Nov. 6, 2006, and an Appeal Brief was filed 5 January, 2007. Prosecution was re-opened by action of the Examiner July 12, 2007. This case is a Division of USPN 6,420,176, which relates to a novel composition of matter. A provisional double-patenting rejection has been made of the inventors' USSN 08/803,484, which relates to a new use for a known class of DNA.

JURISDICTION

This is an appeal under 35 USC 134(a) from a Final Rejection bearing a mail date of April 16, 2008 and setting a shortened 3-month statutory period for reply. A Notice of Appeal together with a petition for a 3-month extension of time and the applicable fee was filed October 16, 2008. Under B. R. 41.37, the due date for this brief is December 16, 2008.

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Pollard H; Remy JS; Loussouarn G; Demolombe S; Behr JP; J Biol Chem 1998 Mar 27;273 (13):7507-11 18

STATUS OF AMENDMENTS

No amendment has been filed after the final rejection. The last paper on behalf of the Applicants was filed December 12, 2007.

GROUNDS OF REJECTION

I. Objection to Claims 23-26, 28, 30-33, 35 and 40-44 under 35 USC § 112, 1st para., New matter, "DNA and a sugar, or polyethyleneimine, or polyethylenimine derivatives."

II. Objection to Claim 30 under 35 USC § 112, 2nd para., molar ratio

III. Rejection of Claims 23-26, 28, 30-32, 35 and 40, 41 and 43-44 under 35 USC 102(e) as being anticipated under Behr (USPN 6,013,240, Jan 11, 2000; 102(e) date=2-28-97) as supported by Liu (Vaccine, 2002, Vol. 20, pg

42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9).

IV. Rejection of Claims 23-26, 28, 30-32, 35, 40, 41, 43 and 44 under 35 USC 103(a) for obviousness over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) and in view of Holler (US Patent 5,908,923).

V. Claims 23-26, 28, 30-33, 35 and 40-43 remain and claim 44 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 08/803484 in view of the disclosure of '484.

VI. Objection to Claims 23-26, 28, 30-33, 35 and 40-44 under 35 USC § 112, 1st para, New matter, "without the use of a needle."

STATEMENT OF FACTS

Introduction

The presently claimed invention relates to a new method of administering a vaccine that does not require use of a needle. (App, p. 25, lines 12-13) It has the advantages of being simple, inexpensive (line 15), applicable to a broad range of diseases (lines 17-21), and painless (lines 24-25). In a key experiment (Example 8), DNA complexed with various materials was applied to the prepared skin on the backs of mice for one hour or subcutaneously, and the results were shown in Table 2 (page 23). In Experiment No. 5 of Example 8, DNA formulated in glucose solution and administered transcutaneously performed sixteen times better than the same formulation administered by subcutaneous injection.

I. Objection to Claims 23-26, 28, 30-33, 35 and 40-44 under 35 USC § 112, 1st para., New matter, "DNA and a sugar, or polyethyleneimine, or polyethylenimine derivatives."

The Examiner has objected that the language in Claim 23 "DNA and a sugar, or polyethyleneimine, or polyethylenimine derivatives," is new matter. In a Preliminary Amendment for this divisional application filed February 21, 2002, the Applicants pointed out that Claims 23-41 corresponded to the original Class II of the parent application USSN 09/153,1578. And indeed, in an

Amendment filed June 7, 2004 at page 6, the applicants pointed out specifically that the Examiner quoted original Claim 8 as including the following language: "wherein the complex is selected from the group consisting of DNA conjugates of sugars, polyethylenimine, polyethylenimine derivatives, and mixtures thereof." Further, the Applicants pointed out Examples 6, 7 and 10 in the parent patent, that include a variety of combinations, including DNA, DNA with PEI, DNA and PEI derivatives (-mannose, -galactose and -glucose), some in saline and some in glucose solution. Applicants now point out that DNA and a sugar, DNA and PEI, and DNA and a PEI-derivative (PEI-man) are all found in Table 2, because all were formulated in a sugar solution (page 22, line 35).

II. Objection to Claim 30 under 35 USC § 112, 2nd para., molar ratio

Claim 30 "The method of Claim 26, wherein the complex comprises a 5:1 ratio of mannosylated polyethylenimine nitrogen per DNA phosphate," has been objected to for lack of clarity. Support for this Claim is found at page 22 of the application, lines 9-16, where, to form a neutral complex, the ratio of PEI-man to DNA is 5:1 (lines 11-12). A different ratio applies if the complex is PEI-DNA. Then the ratio of PEI to DNA is 3:1 (line 12).

At item II, page 5 of an office action dated April 16, 2008, the Examiner has objected that mannosylated polyethylenimine nitrogen is not distinguished

from polyethylenimine nitrogen and that Claim 30 does not clearly limit the complex to having mannosylated polythylenimine, and does not further limit Claim 26.

III. Rejection of Claims 23-26, 28, 30-32, 35 and 40, 41 and 43-44 under 35 USC 102(e) as being anticipated under Behr (USPN 6,013,240, Jan 11, 2000; 102(e) date=2-28-97) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9).

A. Contents of the File Wrapper

This is a new rejection. The original anticipation rejection over Behr in an office action dated March 10, 2004, starting at page 16. In an amendment filed June 24, 2004, the applicants amended the Claims to recite all the limitations of the single claim not subject to the rejection, and the rejection was not withdrawn. Instead, the Carson reference was added to the rejection in an office action dated Sept. 22, 2004, starting at page 23, and stated that the phrase "A method of transfecting antigen presenting cells" was not being given patentable weight because *it may not occur* (emphasis added) at page 24, lines 2-3.

The rejection for anticipation by Behr as supported by Carson, Mittal and Kuby has been withdrawn after the applicants pointed out in a paper filed

December 12, 2007, beginning at page 5 that the basis for the rejection, namely that "A method of transfecting antigen presenting cells" had not been given patentable weight, no longer applied because the base claim had been amended to recite "whereby antigen presenting cells of said skin or mucosa are transfected."

In an office action dated April 16, 2008, the Examiner made a new anticipation rejection, substituting the Liu reference, published in 2002, for the Carson reference. The Examiner acknowledges that the present claims have priority to at least September 15, 1998. See page 6, second full paragraph, last line.

Accordingly, the only difference between the rejections is the addition of the Liu reference, which is not available as prior art against the present claims: therefore, the present rejection must be withdrawn.

The Applicants also point out that the Liu reference is being used as prior art, that is, not to demonstrate an inherent property of a material, but, following the guidance provided by the present application, to add method limitations to the disclosure of the Behr reference. The entire reference, for example, is cited to expand the teachings of the Behr reference from a single word, "topically" to describe a new method of use of an admittedly prior art material, to obtain a result the Examiner has admitted "may not occur."

B. Applicable Law - 35 USC § 102

The Applicants note that the latest set of Examiner's Guidelines was modified in with respect to 102(e)(2), not relevant here, in 2000.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The *identical invention* must be shown in as complete detail as is contained in the ... claim. (emphasis added) The elements must be arranged as required by the claim. MPEP 2131. Multiple references may be used to (a) prove that a reference was an enabling disclosure, (b) explain the meaning of a term, or (c) show that a characteristic not disclosed in the reference is inherent. MPEP 2131.01 The burden is on the Examiner to first show that the claimed composition or machine is disclosed *identically* (emphasis added) by the reference, if an additional reference is to be used to show enablement MPEP 2131.01 I. Extrinsic evidence may be used to explain but not expand the meaning of terms and phrases used in the reference relied upon as anticipatory of the claimed subject matter. MPEP 2131.01 II

The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. MPEP 2112.02

After the identical invention is shown to be disclosed, extrinsic evidence may be used to establish that a reference inherently discloses an invention. To do this, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described *in the reference* [emphasis added], and that it would be so recognized by persons of ordinary skill." "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." (citations omitted) In re Roberts, 169 F.3d 743, 49 USPQ2d 1949 (1999). "We do not see how a disclosure or combination of disclosures leaving one to rely on fortune in choosing the referred to material can function as anticipation. Absent a showing of some reasonable certainty of inherency, the rejection under 35 USC 102 must fall." In re Brink, 419 F.2d 914, 918, 164 USPQ 247 (1970).

IV. Rejection of Claims 23-26, 28, 30-32, 35, 40, 41, 43 and 44 under 35 USC 103(a) for obviousness over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) and in view of Holler (US Patent 5,908,923).

A. Contents of the File Wrapper

This is a new rejection. In a paper dated April 16, 2008 starting at page 8, the Examiner withdrew an obviousness rejection over the Behr reference supported by Carson, Mittal, and Kuby, and light of Holler, based on the amendment adding the phrase "without the use of a needle" to Claim 23. The Examiner admits that the Carson reference was limited to intradermal injection.

The Examiner then made a new rejection, substituting the Liu (2002) reference for the Carson reference. The Examiner acknowledges that the present claims have priority to at least September 15, 1998. See page 9, first full paragraph, last line. Accordingly, the Liu reference is not available as prior art, and the Liu reference is the only difference between the present rejection and the rejection that has been with drawn. Accordingly, the present rejection must be withdrawn. The Liu reference is being used as prior art, as shown by the Examiner's argument that if a set of experiments different from those of Behr are performed in the manner taught by the present application, an immune response taught by Behr to be undesirable will result, as confirmed by Liu.

Since at least June 7, 2004, starting at page 20, the Applicants have pointed out that the rejections over the Behr reference are based on hindsight reconstructions of the claims using single items selected from bare listings in that reference that cannot reasonably be construed so expansively.

To the extent a further rejection might be considered, the Applicants offer the following comments regarding the present invention as compared to the scope and content of the prior art.

The Present Invention

The present invention relates to a method of transfecting antigen presenting cells, the steps comprising, selecting a gene delivery complex that transfects antigen presenting cells, comprising DNA and a sugar, or polyethylenimine, or polyethylenimine derivative, and administering the complex by applying the complex without the use of a needle to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, and whereby antigen presenting cells of said skin or mucosa are transfected.

The Behr Reference

Since at least June 7, 2004, starting at page 20, the applicants have pointed out that the teachings of the references, particularly the Behr reference,

are not so clear and precise as the Examiner suggests. In a paper filed March 27, 2007, the Applicants had pointed out, starting at page 30, that the Behr reference discloses the use of PEI for as an adjuvant for gene therapy. Gene therapy is disclosed to consist in correcting a deficiency or an abnormality (mutation, aberrant expression, and the like) or in effecting the expression of a protein of therapeutic value by introducing genetic information into the affected cell or organ (Col. 1, lines 11-15). Gene therapy is a field distinct from immunotherapy: this reference discloses that immunogenicity, that is, the result obtained by the inventors, is to be avoided in this context (Col. 1, line 51). While both direct injection and topical administration are said to be preferred (Col. 6, lines 5-9), only direct injection is discussed in any detail or shown in any experiments, and there is no disclosure of how to accomplish gene delivery of any sort by means of topical administration.

In a paper filed December 12, 2007, at page 7, the applicants pointed out that the Behr reference teaches only direct injection into the brain for the transfection of neural tissue. The Behr reference does not show transfection of any antigen presenting cells of the skin; indeed the methods described in the Behr reference bypass the skin entirely, and that the distinction between the types of cells transfected, as claimed, is related to the advantages obtained by the invention.

The Applicants pointed out that PEI is said to be useful in a wide variety of cells, (tumor cells, liver cells, haematopoietic cells Col. 5, lines 41-43), but it does not disclose or discuss the transfection of antigen presenting cells. This makes sense because antigen presenting cells give rise to immune responses, that is, immunogenicity, a result that the reference discloses is not desired for its purposes. (Col. 1, line 51) It discusses the use of a wide variety of targeting elements (sugars, peptides, oliconucleotides, or lipids Col. 5, lines 55-57) but does not discuss or disclose the use of such targeting elements for the purpose of transfecting antigen presenting cells; sugars are listed as useful for targeting the asialoglycoprotein receptors (Col 5, lines 64-65), not the mannose receptor of the present set of amended claims. There is disclosure that topical formulations may be made along with every other known kind, ("cutaneous, oral, rectal, vaginal, parenteral, intranasal, intravenous, intramuscular, subcutaneous, intraocular, transdermal, and the like") (Col. 6, lines 1-4) but again, there is no disclosure or discussion of how such a preparation might be made or might be used to transfect antigen presenting cells. The implication, of course, is that the topical application would be used for gene therapy purposes, and not for generating undesired immunity. Both saline (Example 13) and glucose (Example 14) formulations are disclosed, without any distinction as to any advantage that might be obtained. Only direct injection into the brain for

the transfection of neural tissue is shown in any experiments, and there is no disclosure of how to accomplish gene delivery by means of topical administration without the use of needles, or any disclosure whatsoever of the transfection of antigen presenting cells of the skin.

The applicants concluded that the present invention is directed to the transfection of a class of cells that is prominent by omission from the Behr reference, for good reason: the present invention results in what is for the Behr references' purpose, an undesired response.

Applicants now point out that the following reference cited in the application at page 14, line 37-page 15, line 6, Pollard H; Remy JS; Loussouarn G; Demolombe S; Behr JP; J Biol Chem 1998 Mar 27;273 (13):7507-11 states in its abstract that "comparative transfection and microinjection experiments with various cell lines confirm that barriers to gene transfer vary with cell type." And that the following reference cited in the application at page 6, line 8, Arthur, J. F et al. Cancer Gene Therapy. 4:1 17-21, 1997, compared gene transfer methods in DC and melanoma cells with various reporter genes including luciferase (See Fig. 4) and reports that, using lipofection, the level of transfection of dendritic cells was comparable to background noise at page 23, first full paragraph and that, with a viral vector, "gene expression achieved in DCs was always two to four orders of magnitude less than that produced by

melanoma cells" at page 23, second full paragraph. The Arthur reference recommended further study to determine whether any of their methods could be used to effectively transfect dendritic cells at page 23, first full paragraph.

Applicants now point out that Example 14 of the Behr reference, which used DNA in 5% glucose injected into the brains of mice in an attempt to transfect neurons, reportedly failed, (Col. 13, lines 8-10.) but DNA in 5% glucose used in the presently claimed method, that is, applied transcutaneously for the purpose of transfecting antigen presenting cells, performed well. (Experiment 5 of Example 8, page 22, Table 2)

The Applicants now point out that the Behr reference used a luciferase assay (Col. 8, lines 8-12) to demonstrate transfection of cells in the Examples, including a test for cytoxicity in Example 8, Col. 10, lines 1-20. No cytotoxicity connected with luciferase was reported.

Claim Limitations Missing from the Behr reference - Claims 24-26, 28, 30-32, 35 and 40, 41 and 43-44

Among the differences between this reference and the presently claimed invention are that the reference does not disclose the transfection of antigen presenting cells, or the targeting of antigen presenting cells, a most significant subset of cells, and prominent by its omission, or formulations that can be used for needleless, in vivo delivery of genes into any cells, much less antigen presenting cells, or any in vivo method of delivery except injection.

Similarly, the reference does not disclose that glucose and PEI derivatives could be used in the claimed method (Claim 24) or that the PEI derivatives can target the mannose receptor instead of the asialoglycoprotein receptors (Claim 25), or anything about mannosylated polyethylenimine (Claim 26) or the manipulation of electrostatically neutral complexes to target antigen presenting cells (Claim 28) or the specific ratio of PEI to DNA that is preferred for different derivatives (Claims 30 and 42), that the glucose solution can be preferred for targeting antigen presenting cells (Claim 31), or that the range of glucose concentration in a method targeting antigen presenting cells is higher than that disclosed for general use for transfecting neurons in the Behr reference (Claims 32 and 33), or that a further step of receptor stimulation, tissue injury or cell injury might activate antigen presenting cells and therefore enhance a

(disclosed in the Behr reference to be an undesired) immune response (Claim 35), or that a plasmid DNA can be successfully used in the claimed method (Claim 40), or that Langerhans cells can be targeted using the claimed method and materials (Claim 41), or that use of a sugar-modified polyethylenimine would be desirable (Claim 43).

Liu

This 2002 reference confirms some of the teachings of the present application. It is not citeable as prior art against the present claims, which have an admitted priority date of September 15, 1998. This reference is being used as prior art, to show that, if one of the failed materials of the Behr reference (DNA formulated in glucose Example 14) is applied to the skin according to the teachings of the present application, transfection of antigen presenting cells will result. This reference was added, and the Carson reference withdrawn, when the language "whereby antigen presenting cells of said skin or mucosa are transfected" was added to the claim.

Kuby and Mittal

The Examiner has cited these references for the purpose of showing that one of the varieties of the marker gene used in the Behr reference, luciferase, or green fluorescent protein, is immunogenic. The Examiner does not suggest that either of these references disclose or discuss the claimed method of transfection

of antigen presenting cells, or the targeting of antigen presenting cells, or formulations that can be used for needleless, in vivo delivery of genes into any cells, much less antigen presenting cells, or any in vivo method of delivery except injection.

The Holler Reference

USPN 5,908,923 to Holler, et al. discloses and claims a sequence listing for a specific transdominant negative integrase gene which is said to be capable of making at least one cell resistant to a retroviral infection (Abstract). This gene was used in vitro to transfect a lymphoblastoid (cancer) cell line (Example 6, Col. 12, line 18.). The methods of transfection mentioned are calcium phosphate co-precipitation, cationic liposomes, electroporation, receptor mediated endocytosis, naked DNA, transduction by viral vector, and particle-mediated gene transfer. (Col. 7, lines 40-48) The only method discussed, (which is also shown in the Examples) is calcium precipitation.

In a paper filed June 24, 2004, at page 26, the applicants pointed out that the present application discloses that an article published several years later compared transfection rates in antigen presenting cells and a cancer cell line (melanoma) that was known to be readily transfected by all the methods tested. (See Arthur, J. F. et al., Cancer Gene Therapy 4:1 17-21, 1997, page 21, lines 2-4). This article reported only "low efficient" in vitro methods were known at

the time, see page 6, lines 4-11 (cite to Arthur, J. F. et al., Cancer Gene Therapy 4:1 17-21, 1997 and Song, E. S., et al., PNAS USA 94:5, 1943-8, 1997); and that neither they nor the known in vivo methods had been shown to effectively deliver genes to antigen presenting cells, much less delivery of genes through the skin into the Langerhans cells (page 6, lines 16-19).

In an office action dated September 22, 2004, at page 29 stating that Holler taught a plasmid encoding replication defective HIV for use in vivo, and at page 30 the Examiner stated that the Holler reference was being cited to supply an expectation of success, if the procedure of the Behr reference were modified.

The applicants now quote the entirety of the Examiner's citation to Col. 4 lines 51-54: "Thus, in a tenth aspect, the present invention is directed to a method of treating AIDS in a patient comprising administering to said patient a therapeutically effective amount of a transdominant negative integrase gene." The applicants note that this is a statement of potential utility supported only by in vitro experiments in a lymphoblastiod cell line, not dendritic cells.

The Examiner does not suggest that this reference discloses or discusses the claimed method of transfection of antigen presenting cells. The applicants now point out that the Examiner's comment at the bottom of page 10 of the office action dated April 16, 2008 that the combination of Behr, Liu, Mittal and

Kuby with the Holler reference demonstrates a likelihood of success is contradicted by these later references, which disclose that cancer cell lines are easier to transfect than antigen presenting cells. The Arthur reference states at page Col. 2, first full paragraph that they obtained levels of gene expression that were barely detectable above background. In further discussion the authors were unwilling to rule out lipofectamine as a reagent, recommending more testing.

B. Applicable Law - 35 USC § 103

Whether patents are allowable in a given particular field of art is not a question of Patent and Trademark Office discretion but of law, and examiners have no discretion to deny patents to inventions meeting the statutory criteria. Animal Legal Defense Fund v. Quigg, 18 USPQ 2d 1677, 1685, Fed. Cir. (1985).

Office policy is to follow Graham v. John Deere Co. in the consideration and determination of obviousness under 35 U.S.C. 103.

The claimed invention as a whole must be considered. MPEP 2142.01 In determining whether the invention as a whole would have been obvious under 35 U.S.C. 103, we must first delineate the invention as a whole. In delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question... but also to those properties of the

subject matter which are inherent in the subject matter *and* are disclosed in the specification. . . it is this invention as a whole, and not some part of it, which must be obvious under 35 U.S.C. 103." In re Antonie, 559 F.2d 618, 620, 195 USPQ 6,8 (CCPA 1977) (emphasis in original) (citations omitted) MPEP 2141.02 V Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established. In re Rijckaert, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993)

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." In re Linter, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972). Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006). MPEP 2143.01

Where the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of

ordinary skill in the art, considering the degree to which one reference might accurately discredit another. In re Young, 927 F.2d 588, 18 USPQ2d 1089 (Fed. Cir. 1991) MPEP 2143.01 II

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art suggests the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) . A reasonable expectation of success -- that is --a showing that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art. KSR International Co. v. Teleflex Inc., 550 U.S. ___, ___, 82 USPQ2d 1385, 1395 (2007) Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. Ex parte Erlich, 3 USPQ2d 1011 (Bd. Pat. App. & Inter. 1986) MPEP 2143.02 III

If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) MPEP 2143.01 V

If the proposed modifications or combination of the prior art would changed the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); see also MPEP 2143.01 VI.

V. Claims 23-26, 28, 30-33, 35 and 40-43 remain and claim 44 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 08/803484 in view of the disclosure of '484.

These claims have been provisionally rejected of the yet-to-be allowed claims of USSN 08/803,484, filed by the inventors February 20, 1997 and incorporated by reference in the text of the present application as if set forth in full. It is distinguished from the present invention in the text of the application at page 4, line 29 to page 5, line 11. That application relates to the use of a certain kind of genetic material, that is a DNA template from a specific material previously disclosed as ineffective for raising an immune response, namely a replication-defective retrovirus, can be used to raise an immune response, and can be formulated to have added advantages of safety. That application does not disclose or discuss the specific materials or methods of the present

application, or that the complexes of the present application can be used by simply applying them on the skin or mucosa of an animal.

VI. Objection to Claims 23-26, 28, 30-33, 35 and 40-44 under 35 USC § 112, 1st para, New matter, "without the use of a needle."

We believe this rejection has been withdrawn, because the Applicants pointed out in when this amendment was first introduced on December 12, 2007, that this language is supported by the Abstract, and the Examiner has acknowledged in the Final Rejection bearing a mail date of April 16, 2008 at page 3, 1st full paragraph that support is found therein. This rejection was not one of the five rejections listed by the Examiner as being maintained. However, the text at page 3 appears to contain a typographical error, and this section is included to resolve the ambiguity.

ARGUMENT

I. Objection to Claims 23-26, 28, 30-33, 35 and 40-44 under 35 USC § 112, 1st para., New matter, "DNA and a sugar, or polyethyleneimine, or polyethylenimine derivatives."

The present question involves an objection to language in a claim, not an amendment to the abstract, specification, or drawings in the application. Under the published practice of the United States Patent and Trademark Office, claim

language is not properly rejectable as new matter (MPEP 2163.01; MPEP 2163.06, In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

This limitation is supported by the text of the present application at least at page 15, lines 6-8 and 16-17, as well as at Example 10 and Table 2, where DNA, PEI, and PEI derivatives were all formulated in 8% glucose, and that for the transcutaneous method, DNA formulated with sugar only was the most efficient gene delivery system.

This same information can be found in the parent patent, USPN 6,420,176. It is undisputed that this patent discloses the use of DNA combined with PEI, and with PEI modified with various sugars, including mannose, galactose and glucose (in saline solution, Experiment 6, Col. 14, line 63, Table 1), as well as DNA alone, DNA combined with PEI and DNA combined with PEI modified with mannose (formulated in glucose solution, Experiment 8, Col. 15, final line, Table 2) and the surprising results for transcutaneous delivery for DNA complexed with glucose alone is discussed (Example 10). Applicants submit that the claim language cannot reasonably be construed as new matter.

II. Objection to Claim 30 under 35 USC § 112, 2nd para., molar ratio

The applicants would be willing to accept an amendment to Claim 26 that would change its dependency to that of Claim 24, and replace --derivative is--

with "complex comprises DNA and" or any other reasonable and suitable amendment, i.e.,

"26. The method of Claim 24, wherein the complex comprises DNA and mannosylated polyethylenimine."

III. Rejection of Claims 23-26, 28, 30-32, 35 and 40, 41 and 43-44 under 35 USC 102(e) as being anticipated under Behr (USPN 6,013,240, Jan 11, 2000; 102(e) date=2-28-97) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9).

This is a new rejection. In an office action with a mail date of April 16, 2008, the anticipation rejection was withdrawn, and a new rejection was issued, where the Carson reference was been replaced by a newly cited article (Liu). The only difference between the rejections is the Lui reference, published 4 years after the acknowledged priority date of the present claims (at least September 15, 1998) for the proposition that one of ordinary skill in the art, at the time the Behr patent was filed, would know that the claimed topical method would work, even though the claimed method is not found within the teachings of the Behr patent. The Liu reference is unavailable for that purpose, at least because the Examiner has admitted that the transfection of antigen presenting

cells "may not occur.," office action dated Sept. 22, 2004, at page 24, lines 2-3. Because the earlier rejection was distinguished and the only difference between the two rejections was the new (unavailable) reference, the new rejection must also be withdrawn. Technical details of the distinctions between the base reference and the presently claimed invention are discussed in the Statement of Facts and Argument for the Obviousness Rejection, Item IV.

IV. Rejection of Claims 23-26, 28, 30-32, 35, 40, 41, 43 and 44 under 35 USC 103(a) for obviousness over Behr (US Patent 6,013,240, Jan. 11, 2000) as supported by Liu (Vaccine, 2002, Vol. 20, pg 42-48), Mittal (J. General Virol., Jan. 1996, Vol. 77, pg 1-9, abstract only) and Kuby (ed., Immunology, 1992, W.H. Freeman and Company, Chapter 1, "Acquired Immunity," pg 8-9) and in view of Holler (US Patent 5,908,923).

As discussed in the Statement of Facts, the Behr reference is a very general reference that lacks specific disclosure with respect to the insertion of genes into antigen presenting cells, APCs, in part because the function of APCs is to provide an immune system response ("immunogenicity" is undesired in the reference Col. 1, line 51). The present application references publications by the Behr research group (Pollard et al., page 13, line 5 and Zanta, et al., page 22, line 2), and notes that key materials were supplied by Dr. Behr (page 15, line 13), and discloses how to modify the teachings of the Behr reference, to apply it to a new class of cells by targeting a different receptor (Example 6),

manipulating the charge of a complex (Example 7), formulating in sugar solution (Example 10) and using a transcutaneous delivery method (Example 8) to get a new effect (immune response, page 24, line 20) that the inventors, but not Dr. Behr, et al., ("immunogenicity" Col. 1, line 51) desired. Further, in Example 14 of the reference, an attempt to transfect neurons by injecting DNA in 5% glucose into the brains of mice failed (Col. 13, lines 8-10).

The contrast between Example 14 of the Behr reference and performance of DNA in 5% glucose transcutaneously delivered in mice (Experiment 5, Example 8, Table 2, and page 24, lines 29-37) is clear evidence that the limitations of the present claims are related to the advantaged obtained by the invention: the method of administration influences the outcome.

The Examiner points to no teaching or suggestion in the prior art that would establish a likelihood of success in this case. Here, multiple modifications are required, the principle of operation of the prior art invention is changed, and the result is undesired for the purposes of the primary reference. The only teaching on how to modify the Behr reference to obtain the inventors' desired result is found in the present application.

The Examiner's contention that transfection with one type of cell is necessarily an indicator of success with another type of cell is contradicted by references cited in the text of the application. In particular, the Pollard and

Arthur references demonstrate that dendritic cells have historically been more difficult to transfect than cancer cells.

The subsidiary references Mittal, Kuby and Holler admittedly do not fill the gaps in the base reference, because they do not relate to any methods of in vivo gene delivery. The inherency argument by the Examiner is contradicted by the experiments in the Behr reference: Luciferase was used in those experiments and neither undesired immunogenicity or toxicity was found. The application cites references from the text that show that luciferase was commonly used as a reporter gene in papers that did not purport to say that effective transfection of antigen presenting cells had been achieved. Further, Example 14 of the Behr reference shows failure of one set of materials used successfully in the claimed method. In order for the Behr reference to be predictive to the level required by an inherency rejection, that transfection with DNA and sugar injected into neural tissue would have had to have worked. If that transfection had worked, then the purpose of the Behr reference, to demonstrate that PEI is an improved adjuvant for gene therapy, would have failed.

The Liu reference is not prior art, and so is unavailable to supply the missing limitations or show likelihood of success of a modified Behr method.

The Holler reference merely relates to in vitro use of a specific gene, does not fill the gaps in disclosure about the method, and is not cited for that purpose, because it admittedly says nothing about the claimed method. Indeed, this 1994 reference would appear to recommend that the gene can be successfully delivered by any and all methods. (See Holler Col. 7 lines 40-57.) However, the present application discloses that the Arthur reference, an article published several years later, taught that effective delivery of genes into antigen presenting cells had not been accomplished. This teaching is well-founded: the Arthur reference stated that they had obtained results with lipofectamine comparable to background noise, and in further discussion recommends further experimentation with lipofectamine despite the poor results. This is not success. This is a recommendation to try again, using a different technique.

There is no combination of the cited references that yields the claimed invention, at least because the method limitations missing from the Behr reference are admittedly not found in any of the subsidiary prior art references.

V. Claims 23-26, 28, 30-33, 35 and 40-43 remain and claim 44 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 58-71 of copending Application No. 08/803484 in view of the disclosure of '484.

These claims have been provisionally rejected of the yet-to-be allowed claims of USSN 08/803,484, filed by the inventors February 20, 1997, disclosed and distinguished from the present invention in the text of the application. The '804 application relates to the use of plasmid DNA encoding a replication-defective retrovirus instead of the retrovirus itself, for raising an immune response. The presently claimed method of delivering genes into antigen presenting cells of the skin is not disclosed or discussed in that application.

VI. Objection to Claims 23-26, 28, 30-33, 35 and 40-44 under 35 USC § 112, 1st para, New matter, "without the use of a needle."

We believe this rejection has been withdrawn, because the Applicants pointed out in when this amendment was first introduced on December 12, 2007, that this language is supported by the Abstract, and the Examiner has acknowledged in the Final Rejection bearing a mail date of April 16, 2008 at page 3, 1st full paragraph that support is found therein. This rejection was not one of the five rejections listed by the Examiner as being maintained. However, the text at page 3 appears to contain a typographical error, and this section is included to resolve the ambiguity.

APPENDIX

Appendix - Claims

Claims 1-22 (Cancelled)

23. (Rejected and Objected To) A method of transfecting antigen presenting cells, the steps comprising selecting a gene delivery complex that transfects antigen presenting cells, comprising DNA and a sugar, or polyethylenimine, or polyethylenimine derivative, and administering the complex by applying the complex without the use of a needle to the skin or mucosa surfaces of an animal, wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein operatively linked to a promoter, and whereby antigen presenting cells of said skin or mucosa are transfected.

24. (Rejected and Objected To) The method of Claim 23, wherein the complex comprises DNA and glucose or a polyethylenimine derivative.

25. (Rejected and Objected To) The method of Claim 24, wherein the polyethyleneimine derivative targets the mannose receptor found on the surface of antigen presenting cells.

26. (Rejected and Objected To) The method of Claim 25, wherein the derivative is mannosylated polyetheylenimine.

27. (Cancelled).

28. (Rejected and Objected To) The method of Claim 23, wherein the complex is electrostatically neutral.

29. (Cancelled)

30. (Rejected and Objected To) The method of Claim 26, wherein the complex comprises a 5:1 ratio of mannosylated polyethylenimine nitrogen per DNA phosphate.

31. (Rejected and Objected To) The method of Claim 23, wherein the gene delivery complex is added to a glucose solution.

32. (Rejected and Objected To) The method of Claim 31, wherein the glucose solution is 5-10% glucose.

33. (Objected To) The method of Claim 32, wherein the glucose solution is 8% glucose.

34. (Cancelled)

35. (Rejected and Objected To) The method of Claim 23, further comprising one or more steps selected from the group consisting of receptor stimulation, toxin activation, tissue injury and cell injury.

36. - 39 (Cancelled)

40. (Rejected and Objected To) The method of Claim 23, wherein the DNA is a plasmid.

41. (Rejected and Objected To) The method of Claim 23, wherein the cells are Langerhans cells.

42. (Objected To) The method of Claim 44, wherein the complex comprises a 3:1 ratio of polyethylenimine nitrogen per DNA phosphate.

43. (Rejected and Objected To) The method of Claim 23, wherein the derivative is a sugar-modified polyethylenimine.

44. (Rejected and Objected To) The method of Claim 23, wherein the complex comprises DNA and polyethylenimine.

Appendix - Claim Support

Independent Claim 23 {Original Claim 22} – relates to a method of transfecting **{defined page 6, lines 1-2}** antigen presenting cells **{defined page 2, lines 29-31; Title, Abstract. Field of the Invention, page 2, lines 11-24}**, the steps comprising selecting a gene delivery complex **{page 12, lines 32-33 and 35-37}** that transfects antigen presenting cells, comprising DNA **{page 8, line 27}** and a sugar, **{page 24, line 30}** or polyethylenimine, **{page 20, line 10}** or polyethylenimine derivatives **{page 14, lines 20-22; page 21, line 21, Table 1}**, and administering the complex by applying the complex to the skin or mucosa surfaces of an animal **{page 16, line 34; page 23, line 10, Table 2}**, without the use of a needle **{Abstract; page 25, lines 13-14 and 24-25;**

contrasted with injection page 2, lines 18-24 and Fig. 3; procedure described page 22, line 36-page 23, line 1} wherein said DNA comprises a nucleic acid sequence encoding at least one immunogenic protein {**page 8, lines 27-8**}operatively linked to a promoter {**page 19, line 18**}.

24. The method of Claim 23, whererin the complex comprises DNA and glucose {**Original Claim 8, Table 2, Experiment #5page 22, line 35, page 24, lines 36-37**} or a polyethylenimine derivative. {**Table 1**}

25. The method of Claim 24, wherein the polyethyleneimine derivative targets the mannose receptor {**Original Claim 11, Example 6**} found on the surface of antigen presenting cells {**page 4, lines 23-25, page 11, lines 11-13 and 19-21**}.

26. The method of Claim 25, wherein the derivative is mannosylated polyetheylenimine{**Original Claim 9, Table 2**}.

28. The method of Claim 23, wherein the complex is electrostatically neutral {**Example 7, page 21, line 30, page 22, line 5**}.

30. The method of Claim 26, wherein the complex comprises a 5:1 ratio of mannosylated polyethylenimine nitrogen per DNA phosphate {**Example 7, page 22, lines 11-12**}.

31. The method of Claim 23, wherein the gene delivery complex is added to a glucose solution. {**page 24, lines 33-35**}

32. The method of Claim 31, wherein the glucose solution is 5-10% glucose. {**page 22, lines 35-36**}

33. The method of Claim 32, wherein the glucose solution is 8% glucose. {**page 22, lines 35-36**}

35. The method of Claim 23, further comprising one or more steps selected from the group consisting of receptor stimulation, toxin activation, tissue injury and cell injury. {**page 16, lines 36-38**}

40. (Rejected and Objected To) The method of Claim 23, wherein the DNA is a plasmid. {**page 13, line 17**}

41. (Rejected and Objected To) The method of Claim 23, wherein the cells are Langerhans cells. {**page 2, lines 18-20**}

42. (Rejected and Objected To) The method of Claim 44, wherein the complex comprises a 3:1 ratio of polyethylenimine nitrogen per DNA phosphate. {**page 22, lines 10-13**}

43. (Rejected and Objected To) The method of Claim 23, wherein the derivative is a sugar-modified polyethylenimine. {**Original Claim 9 Tables 1 and 2**}

44. (Rejected and Objected To) The method of Claim 23, wherein the complex comprises DNA and polyethylenimine. {**Original Claim 8 Tables 1 and 2**}

Appendix - Drawing Analysis

In Fig. 2, {**page 7, line 7**} the process for sugar-mediated gene delivery into cells expressing mannose-receptors is illustrated conceptually. Target cells (10), in this case, immature Langerhans cells having one or more mannose-receptors (12) are exposed to a gene-delivery complex (13) comprising a polyethylenimine-sugar (mannose) complexed with the foreign genetic material. The gene delivery complex (13) binds to the receptors (12) of the cell (10) and the PEI-man-DNA is incorporated into the cell via endocytosis in an endosome (14). The vector (PEI-man) has the property of breaking (15) the endosome , allowing the foreign genetic material to be released into the cell. The cell matures (16) and expresses proteins (17) coded by the foreign genetic material.

In FIG. 3, {**page 7, line 18**} the experiment demonstrating in vivo the sugar-mediated gene delivery into cells expressing mannose-receptors is illustrated. Target cells are Langerhans cells in the skin known to express mannose receptors. Mice (21) were anesthetized and an area on the back of each mouse (22) was shaved. The shaved surface with ethanol. PEI-man-DNA gene delivery complex in 8% glucose (23) was applied to the shaved area (22) of each mouse. Langerhans cells (24) found in the shaved area of the skin (22) pick up the complex as described in FIG. 2 above, get activated and migrate

(24) to the draining lymph node (25). During the migration Langerhans cells (24) mature to be dendritic cells (26) and express the protein (27) encoded by the DNA.

Fig. 7A-7D {**page 8, line 1**}reports experimental evidence that transcutaneous transduction of Langerhans cells results in migration of the cells and expression of the transferred gene. The figure is a series of color photographs which records green cells having DC morphology and expressing the green fluorescent protein, which is the product of the gene which was transferred via skin delivery. Panel A is a sample of a lymph node from a control mouse at 200x magnification. It exhibits a normal amount of background fluorescence. The same is true of Panel C, except that the magnification is 400x. Panel B is a sample from a lymph node of a mouse that was immunized by the transcutaneous application of a PEI-mannose-DNA complex. Panel D is the same as Panel B, except that the magnification is 400x. The fluorescence exhibits the bumpy morphology characteristic of dendritic cells expressing proteins.

Appendix - Evidence

Experimental Support in the Disclosure

This application discloses experiments that demonstrate the claimed complexes can penetrate the skin and transfect antigen presenting cells in vivo. {**Example**

8, page 22, lines 30-32} Various gene delivery complexes were used: DNA alone, DNA combined with PEI (PEI-DNA) and DNA combined with PEI modified with mannose (PEI-man-DNA), each combined with a sugar {**formulated in glucose solution, Experiment 8, page 22, line 35 , Table 2**}. The complexes are most effectively delivered by a transcutaneous method instead of by injection, and in this Example, the DNA-sugar combination worked best, using the transcutaneous method. This last result is surprising, and shows that sugars can complex the DNA. {**Example 10, page 24, lines 34-35**}

A supporting in vitro experiment uses DNA in combination with PEI, PEI modified with various sugars, including mannose, galactose and glucose {**in saline solution, discussion of Fig. 4, page 7 lines 29-35, Example 6 at page 21 line 15, Table 1**}. Fig. 4 shows that, in vitro and in saline solution, PEI-man is more efficient than PEI. {**Example 7, page 7, lines 29-35. page 22, line 21**}

The application discloses the details of construction of PEI-man {**"isothiocyanantophenyl phenyl mannose derivative, coupled to PEI 25 kDa, yielding a ligand (or, mannose residue of low affinity for the mannose receptor, 1 mM)"; Example 7, page 21, lines 26-27**} the importance of avoiding the asialoglycoprotein receptor {**page 21, lines 28-29**} preferring the mannose receptor {**Example 6, page 21, lines 8-11**} and the different N:P

ratios desired for PEI-man-DNA {**5:1 page 22, lines 11-12**} and and PEI-DNA {**3:1 page 22, line 12**}

The application discloses the best available art for transducing dendritic cells, in vitro use of lipofectamine {**Example 1, page 18, lines 30-31, page 20, lines 27-29**} to deliver genes into antigen presenting cells, and an improvement, use of polyethylenimine (PEI) for that purpose {**Example 5, page 20, lines 28-29**}, also in vitro. The application discloses that both lipofectamine and PEI are toxic to the target cells (dendritic cells) {**Example 5, page 20, lines 30-31**}. The application also discloses that dendritic cells are capable of producing CTL responses {**page 11, lines 19-21**} and dendritic cells transfected in vitro with PEI and a DNA encoding model for a full vaccine {**integration and replication defective HIV-1/LW int- Example 1, page 18, lines 31-32; Example 5, page 20, lines 22-23**} are capable of provoking a CTL response in vitro {**Example 3**}, and in vivo {**Example 4**}.

The present application also discloses how to modify the teachings of the closest prior art, namely the Behr reference USPN 6,013,240, so that the claimed antigen presenting cells can be targeted via the mannose receptor as opposed to the asialoglycoprotein receptor {**at least at page 14, line 37 – page 15, line 15, and Example 6, especially page 21, lines 8-9 (use of sugars) and**

Example 7, especially page 21 lines 28-29 (uncharged particles) and page 22 lines 21-26 (control of charge via relative amount of PEI v. DNA}.

Appendix - Related Cases

The present application is a Division of USPN 6,420,176 re "Composition for Delivering DNA into Antigen Presenting Cells of the Skin." The parent case claims a gene delivery complex comprising DNA and mannosylated polyethylenimine (PEI-man). This composition is demonstrated to be useful for vaccination purposes, and various ways of administering the complex, including injection, are disclosed, see Col. 11, lines 48-51. Subclaims relate to details of the DNA and PEI-man.

The present application claims one method of administering a gene delivery complex, that is, without the use of a needle, or as the inventor prefers, transcutaneous administration. The experiments in this case show that DNA complexes made with a variety of materials, including sugars, PEI and sugar-modified PEI, PEI-man and mixtures thereof, can be applied on the skin without injection (page 16, line 34; Table 2). Note: all the entries in Table 2 were formulated in 8% glucose, see Example 8, page 22, line 35.

These claims have been provisionally rejected of the yet-to-be allowed claims of USSN 08/803,484, filed by the inventors February 20, 1997 and

incorporated by reference in the text of the present application as if set forth in full, and distinguished at page 4, lines 29- page 5, line 11 of the present application. USSN 08/803,484 relates to the use of a certain kind of genetic material, that is DNA encoding a specific material previously disclosed as ineffective for raising an immune response, namely a replication-defective retrovirus, can be used to raise an immune response, and has added advantages of safety. That application does not disclose or discuss the specific materials or methods in vitro or in vivo gene delivery, or that the complexes of the present application can be used by simply applying them on the skin or mucosa of an animal.